REMARKS

Claims 1-3, 5-21, 23-30, 37, 38 and 118-124 were pending. Claim 1 has been cancelled. Accordingly, Claims 2-3, 5-21, 23-30, 37 and 118-124 will be pending upon entry of the present amendment.

Claims 2 and 3 have been amended to longer depend from a cancelled claim. Claims 5, 30 and 37 have been amended to delete references to neutral stabilizing groups. Claim 37 has been amended to recite that the compound is cleavable by TOP. Support for these amendments can be found, for example, in the specification as originally filed at least on page 16, lines 1-18 and on page 10, lines 20-25. Claim 13 has been amended to correct a grammatical error. Claim 28 has been amended to be in independent form. No new matter has been added.

The foregoing claim amendments should in no way be construed as an acquiescence to any of the Examiner's objections and/or rejections, and have been made solely to expedite prosecution of the present application. Applicants reserve the option to further prosecute the same or similar claims in the present or another patent application.

Applicants note with appreciation that claims 28, 119, and 120 were found to be free of the prior art.

Species Election

Applicants respectfully request clarification with regard to the Examiner's withdrawal of claims 18 and 19, both of which encompass Applicants' elected stabilizing group species, succinyl. Succinyl is a dicarboxylic acid and is, therefore, encompassed by claim 18. Furthermore, succinyl (i.e., succinic acid) is among the stabilizing groups listed in the Markush group of claim 19. It is respectfully noted that the terms "succinic acid" and "succinyl" are used interchangeably through out the specification, for example, at least on page 6, paragraph [0079], as is well known in the art.

Rejection of Claims 1-3, 5-9, 11-17, 25, 26, 28, 37, 38, and 119 under 35 U.S.C. § 112, first paragraph

Claims 1-3, 5-9, 11-17, 25, 26, 28, 37, 38, and 119 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. According to the Examiner, "the claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention."

Claim 1 has been cancelled, thus rendering its rejection moot. Applicants respectfully traverse the rejection as it applies to the remaining claims for at least the following reasons.

Claim 5 and its dependent claims are directed to a compound comprising: (1) a therapeutic agent capable of entering a target cell, (2) an oligopeptide of the formula $(AA)_n$-AA^4-AA^3-AA^2-AA^1, and (3) a negatively charged stabilizing group, and (4) optionally, a linker group not cleavable by TOP. Claim 37 and its dependent claims are directed to pharmaceutical compositions containing such compounds.

The Examiner states that the "specification and claims do not provide sufficient variety of oligopeptides embraced by the generic claim, including examples of any oligopeptides where n>3." In addition, the Examiner (quoting the MPEP) also asserts "that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, this is not a sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence."

However, as discussed below, the presently claimed compound is indeed described both functionally and structurally. Moreover, the specification also discloses the correlation between the function and structure of the compound.

I. Oligopeptides

The specification describes in detail how the claimed oligopeptide of the structure formula $(AA)_n$-AA^4-AA^3-AA^2-AA^1 is linked to the stabilizing group at the amino terminus of the oligopeptide, and then is directly linked to the therapeutic agent, or indirectly linked through the linker group at a second attachment site of the oligopeptide. Furthermore, Applicants provide further written description regarding the interrelationship of structure and function of each portion of the claimed compound.

The specification further describes that the oligopeptide can be from four to twenty peptides in length and provides more than one hundred examples of such peptides. (See pages 19-20). Applicants also describe the functional characteristics of the peptide sequence, and more importantly, the function of the blocking amino acid at position P2 (e.g., the amino acid represented by AA^4 in the formula) which is chosen to "maintain the selectivity for cleavage of the prodrug by TOP and inhibit cleavage of the oligopeptide by...other enzymes in that portion of the oligopeptide most closely linked...to the therapeutic agent portion of the prodrug compound." Therefore, Applicants clearly link the structure of the oligopeptide, and its function within the claimed compounds.

The Examiner notes that "the MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass that genus." Applicants again emphasize that they have described over one hundred different species with their claimed genus of oligopeptides. Clearly, this should be considered a sufficient representative number.

II. Therapeutic Agents

The Examiner further asserts that the while Applicants' specification and claims "provide for a variety of therapeutic agents which are anticancer agents, the specification and claims do not provide sufficient variety in structure to describe all therapeutic agents capable of entering a target cell which are not used in cancer therapy."

Applicants respectfully disagree. The specification describes a broad variety of therapeutic agents which can be employed in the claimed prodrug compounds. All of these agents have well-known and art-recognized structures. For example, the specification describes several well-known anti-inflammatory agents (see, page 22, lines 12-19), as well as anticancer agents.

Indeed, it is firmly established that the descriptive text needed to meet the Written Description requirement varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence (Capon v. Eshhar, 418 F.3d 1349, 2005). Recently, the CAFC in Capon pointed out that "since the law is applied to each invention in view of the state of the relevant knowledge, its application will vary with differences in the state of the predictability of the science." The Court further explained that the Written Description requirement may be satisfied "if in knowledge of the art the disclosed function is correlated to a particular, known structure."

In the present case, the claims encompass therapeutic agents which are well known in the art and have particular, known structures. Thus, according to recent CAFC case law, the structures need not be described in the specification to meet the Written Description requirement. Moreover, the art of linking such agents to peptides, as described by Applicants is also well known and predictable. Therefore, the presently claimed compounds should be considered sufficiently described.

III. Stabilizing Groups

The Examiner acknowledges that the "specification and claims provide examples of negatively charged and esterified dicarboxylic acids as the stabilizing group." However, the Examiner asserts that the claims and specification "are silent to the myriad of compounds embraced by neutral stabilizing groups."

Applicants respectfully disagree. However, to expedite prosecution, the present claims have been amended to delete references to neutral stabilizing groups. Moreover, with respect to such stabilizing groups, the specification links the structure of the stabilizing groups to their function by teaching that the stabilizing group serves to "protect the prodrug from cleavage in circulating blood when administered to the patient" (page 15, lines 13-15). Further, Applicants describe the structure of the moiety at pages 15, line 21 through page 16, line 20. In addition, it would be understood by a person of ordinary skill in the art that certain chemical characteristics, such as charge, directly relate to the ability of the stabilizing group to perform its intended function, e.g., protect the prodrug from cleavage in circulating blood, without cause toxicity due to aggregation of the prodrug in the patient. Therefore, Applicants clearly describe the function, the structure, and the inter relation of the structure and function in the present specification for the stabilizing group in the specification as originally filed.

IV. Target Cell Associated Enzymes

According to the Examiner, the specification and claims provide for the target-cell-associated enzyme to be TOP, but do not provide any examples to describe a non-TOP enzyme associated with a target cell. Applicants submit that as currently amended, Applicants claim compositions and methods where the target-cell-associated enzyme is TOP. Applicants submit the specification and claims adequately describe compositions wherein the target cells are associated with TOP, as acknowledged by the Examiner.

Overall, the Written Description requirement must be appreciated in the context of the particular invention and the state of that knowledge (Capon at 1358). In the present case, the invention involves the production of prodrug conjugates by selecting and linking peptides to therapeutic agents using negatively charged stabilizing groups. While the discovery that such stabilizing groups were highly beneficial was entirely inventive, the state of the knowledge with respect to selecting and linking the peptides, as described by Applicants, was well established and highly predictable. The Written Description requirement states that the Patentee must describe the invention, it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution (Capon at 1358).

For at least the foregoing reasons, Applicants respectfully request that this rejection of the claims under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejection of Claims 1-3 5-9, 11-17, 25, 26, 30 and 118 under 35 U.S.C. § 103(a)

Claims 1-3, 5-9, 11-17, 25, 26, 30 and 118 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Trouet *et al.* (5,962,216), in view of Veronese (U.S. Patent No. 5,286,637), Dalborg (U.S. Patent No. 6,048,720), Gaetner *et al.* (*Bioconj. Chem.* (1996) 7(1), pages 38-44), and Inada *et al.* (*Methods Enzymol.* (1994) 242, pages 65-90). Claim 1 has been cancelled, thus rendering its rejection moot. Applicants respectfully traverse this rejection as it applies to the remaining claims.

In particular, claim 5 and its dependent claims are directed to compounds comprising a negatively charged stabilizing group.

The primary reference, Trouet *et al.*, fails to teach or suggest conjugates comprising a negatively charged stabilizing group as presently claimed by Applicants. Moreover, the claimed conjugates have different and unexpected properties compared to conjugates without negatively charged stabilizing groups. Specifically, as shown in Applicants' specification, the presently claimed conjugates possess unexpected functional properties compared to conjugates without a neutral or negative stabilizing group. This is evidenced for example, by the sharp reduction of acute toxicity of N-succinylated βAla-Leu-Ala-Leu-Dox, as compared to the non-succinylated βAla-Leu-Ala-Leu-Dox. Such reduced toxicity could not have been predicted over the teachings of Trouet *et al.* or any other prior art. Nor did Trouet *et al.* or the prior art provide any reasonable expectation of success in achieving a conjugate having such reduced toxicity.

Indeed, Applicants note that the conjugates described in Trouet *et al.* were found to be acutely toxic. For example, when non-succinylated βAla-Leu-Ala-Leu-Dox was administered to five mice at a dose of 174 μMol/ml, all five mice died as described in Example 23 on pages 64-65 of the specification. In contrast, Applicants made the surprising discovery that by attaching a neutral or negatively charged stabilizing group to the conjugate, the acute toxicity of the conjugates were reduced. Specifically, in Example 23 on page 65 of the present specification, Applicants show that capping the terminal amino group of βAla-Leu-Ala-Leu-Dox with a negatively charged moiety resulted in the complete disappearance of the acute toxicity at dose levels as high as 250 mg Dox-HCl, eq./kg.

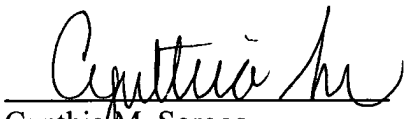
The secondary references, Veronese, Dalborg, Gaertner, and Inada, each fail to overcome the deficiency of the primary reference, Trouet *et al.*, for failing to teach or suggest the use of a negatively charged stabilizing group. In fact, each of these references teach the use of PEG, a neutral stabilizing group. None of the secondary references, alone or in combination, over come the deficiencies of the primary reference by teaching or suggesting the use of a negatively charged stabilizing group.

Therefore, Applicants respectfully request that this rejection of the claims under 35 U.S.C. § 103(a) be withdrawn.

SUMMARY

It is respectfully submitted that this application is in condition for allowance. If there are any remaining issues or the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Respectfully submitted,
LAHIVE & COCKFIELD, LLP



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Date: January 3, 2006